UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,883	05/14/2001	Lex M. Cowsert	ISPH-0576	9012

36441 7590 06/27/2003

MARY E. BAK
HOWSON AND HOWSON, SPRING HOUSE CORPORATE CENTER
BOX 457
SPRING HOUSE, PA 19477

EXAMINER
ZARA, JANE J

ART UNIT	PAPER NUMBER
1635	16

DATE MAILED: 06/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/854,883	Cowsert et al
Examiner	**Art Unit**
Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 7, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, 4-20, 22, 25, 26, 29-32, 37, 38, and 41-49* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *22, 25, 26, 29-32, 37, 38, 45-47, and 49* is/are allowed.

6) ☒ Claim(s) *1, 2, 4-20, 41-44, and 48* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *11,14*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communication filed February 7, 2003, Paper No. 12.

Claims 1, 2, 4-20, 22, 25, 26, 29-32, 37, 38, 41-44 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection not repeated in this Office action is hereby withdrawn.

Response to Arguments and Amendments

Maintained Rejections

Claims 14 and 41-44 are rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed, for the reasons of record set forth in the Office action mailed November 5, 2002, Paper No. 10.

Applicant's arguments filed February 7, 2003 have been fully considered but they are not persuasive. Applicants argue that the mouse model is an accepted clinical model for the demonstration of therapeutic efficacy in other mammals, and furthermore that extrapolation from in vitro to in vivo target gene inhibition is not unpredictable. The applicability of the mouse model as an acceptable clinical model for other mammals is not being disputed in the instant rejection. Rather, the ability to reduce blood glucose levels or delay the onset of increasing glucose levels is not representative of the ability to prevent (e.g. for undefined timespan) any

increase in glucose levels in any animal following administration of antisense that targets and inhibits the expression of PTP1B. The ability to inhibit the expression of the target gene PTP1B in vitro or in vivo using antisense does not predictably prevent any and/or all increases in blood glucose levels in an organism. Therefore, the claims are rejected for lacking enablement over the scope claimed.

In addition, amended claim 14 is drawn to methods of modulating PTP1B expression comprising the administration of antisense. Modulation comprises the ability to increase and decrease target gene expression. No evidence has been provided for the ability to increase the expression of target gene PTP1B expression following the administration of antisense. And the ability to inhibit expression of a target gene in vitro or in vivo comprising administration of antisense that specifically bind to the target gene is not predictive of the ability to increase the expression of a target gene. Therefore, the claim is rejected for lacking enablement over the scope claimed.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-20 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Huang et al, Olefsky and Chernoff et al, in view of Milner et al and Baracchini et al insofar as the claims are drawn to compositions and methods for the inhibition of PTP1B (SEQ ID NO: 243) in vitro comprising the administration of antisense oligonucleotides between 8-50 nucleobases in length that specifically target and inhibit the expression of PTP1B, and which antisense oligonucleotides comprise a phosphorothioate internucleotide linkage, a 2'-O-methoxyethyl sugar moiety, a 5-methylcytosine and which antisense oligonucleotide is a chimeric oligonucleotide, and which target cells include human, rat, mouse and monkey cells, which are liver, kidney or adipose cells.

Huang et al teach antisense oligonucleotides between 8-50 nucleobases in length which inhibit the expression of PTP1B in rat cells in vitro (See entire abstract).

Olefsky teaches antisense oligonucleotides between 8-50 nucleobases in length which inhibit the expression of PTP1B in target cells in vitro (abstract; column 5, lines 23-65).

Chernoff et al teach the nucleotide sequence encoding human PTP1B, and detection of PTP1B expression in mouse cells and in human liver and kidney cells (of SEQ ID NO: 243) (abstract; page 2735; nucleotide sequence in figure 2, page 2737; and figure 4 on page 2738).

The primary references of Huang et al, Olefsky and Chernoff et al do not teach antisense oligonucleotides which target and inhibit PTP1B expression in human, mouse or monkey liver, kidney or adipose cells, and which oligonucleotides further comprise phosphorothioate internucleotide linkages, sugar or nucleobase modifications, nor chimeric antisense molecules.

Milner et al teach the screening of antisense oligonucleotides for their ability to inhibit a target gene of known nucleotide sequence in vitro (See entire text, especially).

Baracchini et al teach chimeric antisense as well as phosphorothioate internucleoside, 2'-O-methoxyethyl sugar, 5-methyl cytosine nucleobase modifications in antisense oligonucleotides (See especially column 6, line 18-column 8, line 56).

It would have been obvious to one of ordinary skill to design and use antisense molecules for the specific inhibition of PTP1B expression, since the sequence for PTP1B was taught previously by Chernoff *et al* and antisense inhibition of PTP1B was taught previously by both Huang et al and Olefsky. One of ordinary skill in the art would have been motivated to inhibit PTP1B because it had been taught previously by Olefsky that aberrant expression of PTP1B was associated with some forms of diabetes and cellular hyperproliferation. One of ordinary skill in

the art would have expected that antisense molecules targeting translated and untranslated regions of the PTP1B gene would inhibit PTP1B expression, and the methods for screening such antisense molecules had been taught previously by Milner et al and were performed routinely in the art. One of ordinary skill in the art would have expected that antisense would inhibit the expression of PTP1B in rat, mouse, monkey and human target cells in vitro, including liver and kidney cells, because Chernoff et al taught the expression of PTP1B in mouse cells and in human liver and kidney cells, and Huang et al and Olefsky taught the inhibition of expression of rat PTP1B using antisense in vitro. It would have been routine experimentation to inhibit the expression of PTP1B in vitro in various target cells by administration of antisense oligonucleotides, which target cells are obtained from various organisms. One of ordinary skill in the art would have been motivated to test for expression and in vitro inhibition of expression of PTP1B in various target cells obtained from various organisms such as rat, mouse, monkey and human because rat, mouse and monkeys have been routinely tested as appropriate in vitro and animal models before testing in humans, for potential efficacy of antisense therapy, and expression of the target PTP1B gene has been taught previously to occur in liver and kidney cells in humans by Chernoff et al. One of ordinary skill in the art would have been motivated to incorporate internucleotide, sugar and nucleobase modifications into such antisense molecules because it had been taught previously by Baracchini *et al.* that such modifications enhance target binding, antisense stability and cellular uptake of antisense oligocucleotides. One of ordinary skill in the art would have expected that the incorporation of such modifications into antisense

molecules would render them less accessible to nuclease degradation, because this had been taught previously by Baracchini *et al.*

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

Claims 22, 25, 26, 29-32, 37, 38, 45-47, 49 appear free of the prior art.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

June 23, 2003

KAREN LACOURCIERE
PATENT EXAMINER